REMARKS

The claims have been amended to point out the invention more distinctly. As applicants have elected to prosecute claims directed to the α_{1I} subunit, the claims now conform to this. SEQ. ID. No.: 28 is the full-length rat α_{1I} subunit; support for subunits with at least 95% homology to this subunit is found on page 8, line 10. No new matter has been added and entry of the amendment is respectfully requested.

Applicants appreciate their attention being called to the error in the serial number of the grandparent application; this has been corrected.

Turning now to the specific grounds for rejection, applicants' responses are as follows:

The Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 2 and 14 were considered indefinite because the name α_1 subunit of mammalian T-type calcium channel was said not to have been defined so as to allow the metes and bounds of the claims to be determined. This has been addressed by amendment as supported as noted on page 8 of the specification. As requested, the claims have been amended to refer to the SEQ. ID. Number.

The objection to claim 3 has been obviated by its cancellation. It is believed that the amendment to claim 14 addresses the further rejection of that claim as well. Accordingly, withdrawal of this basis for rejection is proper.

The Rejections Under 35 U.S.C. §§ 101/112

Claims 1-6 and 14 were rejected as assertedly lacking utility. The utility of the claimed recombinant materials is clearly set forth in the application. As noted on page 5, lines 9-19, the recombinant materials for the α_1 subunits claimed produce functional calcium channels (T-type) that can be used to evaluate the effects of pharmaceuticals and/or toxic substances on these channels. The resulting identified compounds are useful in treating specified conditions: epilepsy, sleep disorders, mood disorders, cardiac hypertrophy, arhythmia and hypertension. Antisense nucleotide sequences are also included (*e.g.*, those included in claims 14 and 18). The utility of the recombinant materials of the invention is further discussed on page 9 of the specification, lines 11-28, for example.

The rationale adduced for stating that these utilities are not substantial or specific is not understood. It certainly seems substantial to be able to identify pharmaceuticals that would be useful in treating the indicated disorders. It is certainly specific since these specified disorders are associated with these calcium ion channels. What the Office really seems to be saying is that this utility is not credible - *i.e.*, the Office simply does not believe that pharmaceuticals identified in this way would be useful in treating the conditions that applicants have stated would be treated. The only reason given by the Office is that "neither the specification nor the art of record disclose any instances where blocking any effects of said channel protein encoded by the DNA of SEQ. ID. No.: 23 reduces the effect of a disease state."

As to the specification, of course, this is simply untrue. The indicated portion of the specification specifically states that these pharmaceuticals would be thus useful. As to the prior art, since SEQ. ID. No.: 23 is not part of the prior art, it is hardly reasonable to expect that the prior art would indeed disclose this. If SEQ. ID. No.: 23 were disclosed in the prior art, applicants would not be filing a patent application to cover it.

In addition, it is simply not true that the art fails to disclose any compounds that can treat disorders associated the T-type calcium ion channels such as those described in the application. Thus, for example, U.S. patent 6,309,858 notes in column 19, lines 63-67, that candidate compounds (*i.e.*, those compounds that are shown to block T-type calcium channels) are useful in the treatment of pain of various types. This application further notes that some compounds are already known to block T-type calcium channels such as ethosuximide and analogs thereof (col. 18, l. 35).

U.S. patent 6,358,706 discloses in column 17 a multiplicity of disorders, including those listed in the present application, that can be treated by compounds that modulate T-type calcium ion channel activity.

In addition, it is believed that the approach taken by the Office in this case is inconsistent with the legal standards set forth by the Federal Circuit to support utility. The Court's position on this is clearly given in *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995). It will be recalled that the claims in *Brana* were directed to compounds useful in treating certain cancers.

The Court made clear that the Office must provide some reason to doubt the teachings of the specification unless they are inherently unbelievable or involve implausible scientific

principles citing *In re Jolles*, 628 F2d 1322, 206 USPQ 885, 890 (CCPA 1980), at page 1441. The Court states at page 1442-1443

> Usefulness in patent law and in particular in the context of pharmaceutical inventions, necessarily includes an expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures of many crucial areas such as the treatment of cancer.

Thus, it is not the law, as the Office would have it, that "utilities that require or constitute carrying out further research to identify or reasonably confirm a 'real world' context of use are not substantial utilities." The *Brana* Court explicitly makes clear that further research and development may be required.

The posture of the Court in *Brana* is entirely consistent with the earlier holdings as the Court itself stated on page 1439 referring to, for example, *Cross v. Iizuka*, 224 USPQ 739 (Fed. Cir. 1985) and *In re Krimmel*, 130 USPQ 215 (CCPA 1961) among others.

In *Cross*, the issue was whether Iizuka was entitled to the benefit of the Japanese priority document when the priority document contained only *in vitro* data showing that the claimed compounds inhibited thromboxane synthetase in human or bovine platelet microsomes. In view of this *in vitro* activity, the specification stated that the compounds would be useful in treating conditions such as inflammation, hypertension, thrombus, cerebral apoplexy, and asthma.

In agreeing with the Board that the disclosure was adequate to support a real world utility, the Court stated

> We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for a compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an important benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility.

(Citing *Nelson v. Bowler & Crossley*, 626 F2d 853, 206 USPQ 881, 883 (CCPA 1980).)

This is precisely applicable here where applicants are providing the very *in vitro* screen which enables the downstream application of compounds that pass this screen.

In *Krimmel*, the Court explicitly held that claims to compounds said, in the specification, to be useful for treating inflammation showed sufficient utility and enablement in light of affidavits showing efficacy in animals. Although the Office argued that the ultimate desire was treatment in humans, the Court rejected this argument. It stated

> There is nothing in the patent statute...which gives the Patent Office the right or duty to require an applicant to prove that compounds or other materials which he is claiming and which he has stated are useful for pharmaceutical applications are safe, effective, and reliable for use with humans.

Similarly, in *Burroughs Wellcome Co. v. Barr Laboratories, Inc.*, 40 F3d 1223, 32 USPQ2d 1915 (Fed. Cir. 1994), cert. denied, 115 S. Ct. 2553 (1995) inventors at Burroughs Wellcome had prepared a patent application directed to using AZT to treat patients infected with HIV on the basis of data obtained only with respect to murine retroviruses in culture. The inventors sent samples of AZT to NIH for determination as to whether the compound was effective against the human counterpart, HIV. When these results were positive, the draft application was filed. The Court held that the workers at NIH were not co-inventors since the patent application, prepared in the absence of these results, was a constructive reduction to practice.

The holding in *Burroughs Wellcome* is instructive for two reasons. First, it shows that there is no requirement that experimental proof of the ultimate desired utility be set forth in the specification. Second, it stands for the proposition that results with respect to analogous materials are supportive of results for a referent material even very early on. In other words, results with regard to murine retroviruses disclosed in the specification were adequate to support a claim to treatment with respect to the analogous viruses in humans; even to the extent that no actual *in vivo* testing was done at all. Only human cell lines were used even by the NIH.

The *Burroughs Wellcome* Court considered claims to treating HIV complete and supported when 1) there was no showing that AZT would be helpful in treating HIV *per se*, and 2) there was no showing that the most relevant screening test (of HIV in human cell lines) had been done. In light of this, it is hard to see how the disclosure of the present application is inadequate when the claims are directed simply to a method for identifying compounds that will

be useful in treating diseases that are mediated by the calcium ion channel that is used in the screen, and the nature of these diseases is disclosed.

Finally, the history of the application at issue in *In re Cortright*, 49 USPQ2d 1464 (Fed. Cir. 1999) is enlightening. The claims in that case were directed to a method of treating baldness using a commercially available product (used to soften cow udders) by applying the product to a human scalp. There was a rejection under § 101 initially, which was overturned by the Board on the basis that the Examiner did not set out sufficient reasons for finding Cortright's statements of utility incredible and further noted "there is no *per se* requirement for clinical evidence to establish the utility of any invention."

In addition, the Court further emphasized, as the Court has consistently done, that

> The PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO *provides evidence* showing that one of ordinary skill would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility (citing *Brana*).

The Court further stated that

> The PTO may establish a reason to doubt an invention's asserted utility when the written description suggests an inherently unbelievable undertaking or involves implausible scientific principles.

Here, there is no inherently unbelievable undertaking or implausible scientific principle involved. Respectfully, applicants believe that the Office has provided no evidence or reason to doubt the invention's asserted utility. It should be clear from the cases cited that a mere assertion that statements contained in the specification are inadequate is not sufficient to reject the present claims.

The Office has shown no reason why applicants' statements - that compounds shown to modulate T-type calcium ion channel activity would be useful in treating epilepsy, sleep disorders, mood disorders, cardiac hypertrophy, arhythmia and hypertension are scientifically implausible or violate scientific principles. Indeed, there is evidence of record that this is entirely the expectation of the art. Certainly no evidence has been adduced to show that these utilities are not credible. As to specificity and substance, the conditions outlined are entirely

specific and certainly important - *i.e.*, substantive. Accordingly, this basis for rejection may properly be withdrawn.

The Rejection Under 35 U.S.C. § 112, First Paragraph, Based on Lack of Written Description

All claims were rejected as purportedly failing to meet the written description requirement. This basis for rejection has been addressed by amendment. It is believed that the claims as presently proposed are consistent with the PTO's guidelines. Attention is called, for example, to example 14 in the training materials associated with these guidelines. As in the exemplified claim, the claimed subject matter is described in terms of both function and structure. The function is that of a T-type calcium channel α_1 subunit and the structure requires that the subunit be at least 95% homologous to the disclosed sequence. The example is thus exactly analogous to the subject matter claimed.

Further, applicants wish to call the attention of the Office to the extensive discussion of conserved regions and characteristic structural features of the α_1 T-type subunits claimed. This discussion begins on page 7, at line 6 and continues to page 8, line 20. It is thus not true that the disclosure "fails to describe the common attributes or characteristics that identify members of the genus." Respectfully, applicants invite the Office to read the disclosure in the specification.

For the reasons stated above, the rejection based on an asserted lack of written description may properly be withdrawn.

CONCLUSION

1. The formal requirements set forth in the Office action have been met; a submission in compliance with the sequence rules is enclosed as is a set of corrected drawings and appropriate amendments.

2. The rejection under 35 U.S.C. § 112, paragraph 2, has been obviated by amendment; the α_1 subunits for which the recombinant materials are now claimed are structurally related by specified homology to the rat α_{1I} subunit, consistent with applicants' election.

3. The Office has provided no evidence or rationale for doubting the statements of utility of the assay methods that can be performed using the recombinant materials of the invention. Unless the Office does so, no *prima facie* case can be acknowledged.

4. The claims as amended comply specifically with the guidelines on written description; the rejection on the basis of lack thereof may properly be withdrawn.

Accordingly, it is believed claims 1-2, 4-6, 14 and 18 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 381092000721.

Respectfully submitted,

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EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please amend paragraph 1, on page 1, lines 2-6, as follows:

This application is a continuation-in-part of application No. 09/346,794 filed 2 July 1999 which is a continuation-in-part of application No. [09/030,428] 09/030,482 filed 25 February 1998 which claims priority from Provisional Application No. 60/039,204 filed 28 February 1997. The disclosures of these applications are incorporated by reference herein.

In the Claims:

1. (Amended) A recombinant DNA molecule which comprises an expression cassette wherein said expression cassette comprises a nucleotide sequence encoding a T-type calcium channel α_1 subunit, said encoding sequence operably linked to control sequences to effect its expression; wherein said α_1 subunit has an amino acid sequence at least 95% homologous to SEQ. ID. No.: 28.

2. (Amended) The DNA molecule of claim 1 wherein said α_1 subunit [is α_{1G}, α_{1H}, or α_{1I}] has the amino acid sequence of SEQ. ID. No.: 28.

4. (Amended) Recombinant host cells modified to contain the DNA molecule of [any of claims 1-3] claim 1.

14. (Amended) An [oligonucleotide] isolated nucleic acid molecule which [consists essentially of] comprises a nucleotide sequence [characteristic of] encoding a T-type calcium channel [α_1] α_{1I} subunit or its complement, [said oligonucleotide coupled to or comprising a detectable label] wherein said α_1 subunit has an amino acid sequence at least 95% homologous to SEQ. ID. No.: 28.

Example 14: Product by Function

Specification: The specification exemplifies a protein isolated from liver that catalyzes the reaction of A → B. The isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO: 3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.

Claim:

A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A → B.

Analysis:

A review of the full content of the specification indicates that a protein having SEQ ID NO: 3 or variants having 95% identity to SEQ ID NO: 3 and having catalytic activity are essential to the operation of the claimed invention. The procedures for making variants of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art.

A review of the claim indicates that variants of SEQ ID NO: 3 include but are not limited to those variants of SEQ ID NO: 3 with substitutions, deletions, insertions and additions; but all variants must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO: 3. Additionally, the claim is drawn to a protein which **comprises** SEQ ID NO: 3 or a variant thereof that has 95% identity to SEQ ID NO: 3. In other words, the protein claimed may be larger than SEQ ID NO: 3 or its variant with 95% identity to SEQ ID NO: 3. It should be noted that "having" is open language, equivalent to "comprising".

The claim has two different generic embodiments, the first being a protein which comprises SEQ ID NO: 3 and the second being variants of SEQ ID NO: 3. There is a single species disclosed, that species being SEQ ID NO: 3.

A search of the prior art indicates that SEQ ID NO: 3 is novel and unobvious.

There is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO: 3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity. One of skill in the art would conclude that

applicant was in possession of the necessary common attributes possessed by the members of the genus.

Conclusion: The disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention.